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(54) ACTIVATED VITAMIN D 3? EMULSION-TYPE LOTIONS

(57) The present invention provides a pharmaceutical composition for local administration in the form of an emulsion that contains active vitamin D₃ and is suitable for application to areas with (the) hair, while also having satisfactory pharmacological activity, primary drug stability and physical stability. This lotion contains (a) a therapeutically effective amount of active vitamin D₃, (b) an oil phase component containing a solid oil component comprising white Petrolatum and a higher alcohol and a liquid oil component comprising squalane, (c) an aqueous phase component containing ionic polysaccharide, and (d) nonionic surfactant; wherein, (1) the content of said ionic polysaccharide is 0.3-1.0 parts by weight of the entire preparation, (2) the content of said higher alcohol is 0.2-1.0 parts by weight of the entire preparation, and (3) the HLB of said nonionic surfactant is 10 or more.

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Description**Field of the invention**

5 [0001] The present invention relates to an active vitamin D₃ emulsion lotion, and more particularly, to an active vitamin D₃ emulsion lotion comprising a specific oil phase component, a specific aqueous phase component, and a nonionic surfactant; wherein, a ionic polysaccharide contained in the aqueous phase component is of a specific content, a higher alcohol contained in the oil phase component is of a specific content, and an HLB of said nonionic surfactant is of a specific value.

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Background Art

[0002] Since, for example, 1 α ,25-dihydroxycholecalciferol or 1 α ,24-dihydroxycholecalciferol is a substance that exhibits Ca regulatory action known to be a physiological action of vitamin D₃, it is referred to as active vitamin D₃. Although the physiological action of active vitamin D₃ is diverse, probably regarding the differentiation inducing action and growth inhibitory action of active vitamin D₃, findings have been obtained which state that the active vitamin D₃ is effective against psoriasis which is a refractory skin disease, by a mechanism which normalizes the undifferentiation and accelerated growth of epidermal cells which are considered to be the cause of this disease (see T. Matsunaga, et al., *J. Dermatol.*, Vol. 17, No. 3, p. 135 (1990)).

20 [0003] Since skin diseases such as psoriasis are diseases of the epidermal layer of the skin outer layer, local administration rather than systemic administration in the form of oral administration or injections and so forth is more advantageous in terms of bioavailability. Moreover, this type of administration is also preferable since it is possible to prevent systemic adverse side effects. Examples of drug forms for local administration include semi-solid preparations such as ointments and creams; liquid preparations such as lotions and liniments; tapes; poultices and powders. However, the semi-solid preparations or liquid preparations are preferred in consideration of the pathology of psoriasis.

[0004] Known examples of semi-solid preparations include an oily ointment having 1 α ,24-dihydroxyvitamin D₃ for its primary drug and white Petrolatum for its base (Japanese Examined Patent Publication No. 3-68009), a cream preparation containing an oil phase component comprising a viscosity adjuster such as cetyl alcohol and a lipophilic solubilizer such as liquid paraffin, a surfactant such as sorbitan monostearate (span 60), and an aqueous phase component such as propylene glycol (Japanese Unexamined Patent Publication No. 4-210903), and an O/W emulsion ointment having 1 α ,24-dihydroxyvitamin D₃ for its primary drug, and containing an oil phase component comprising a solid oil component such as white Petrolatum, a surfactant comprising sodium laurylsulfate, etc., and an aqueous phase component comprising propylene glycol, etc. (Japanese Examined Patent Publication No. 3-68009). In addition, an example of a known cream preparation has 1 α ,24-dihydroxyvitamin D₃ for its primary drug, and contains a solid oil component comprising white Petrolatum, etc., an oil phase component containing a liquid oil component comprising squalane, etc., a surfactant such as polyoxyethylene hydrogenated castor oil 60, and an aqueous phase component such as propylene glycol (specification of WO95/6482).

[0005] However, when considering the pathology of skin diseases, lotion preparations are preferable as preparations for local administration. Since roughly 1/3 of the patients in which psoriasis occurs on the scalp in particular have the hair, lotions are preferable which do not become sticky at locations where there is (the) hair, are easily applied, and have the optimum viscosity for inhibiting running (having, a viscosity of 500 to 1400 mPa · s when measured with a Brookfield rotational viscometer using a spindle no. LV4, at 60 rpm and 25°C). In addition, it is desirable that this viscosity not be easily affected by external stimulation such as temperature or vibrations so that it remains constant at all times. Moreover, since the pathology of psoriasis involves an abnormality in which epidermal cells of the skin are destroyed, and since it is predicted that there is weak resistance to irritating substances, it is preferable that preparations used for psoriasis have a low level of irritation.

[0006] In general, lotions are roughly classified into solution-type lotions and emulsion-type lotions.

[0007] Of active vitamin D₃ lotions, solution-type lotions of calcipotriol or 20(R)-22-oxa-vitamin D₃ derivative are disclosed in the specification of WO91/12807 and the specification of WO92/01454. Since these lotions use a solvent such as ethanol giving a low viscosity to the lotion, not only do they run easily when applied preventing the preparation from effectively remaining at the affected area, but also when applied to the hairline or the forehead, there is a problem of the preparation getting into the eyes. In addition, there is also concern over the irritability of organic solvents such as ethanol used as solvent or absorption enhancer.

[0008] An example of an emulsion-type lotion is described, for example, in Japanese Unexamined Patent Publication No. 60-174705, and is composed of active vitamin D₃ and its derivatives, an oil phase component such as spermaceti wax, cetanol, Petrolatum or squalane, a surfactant such as polyoxyethylene (10 mol) monostearate or sorbitan monooleate, and an aqueous phase component such as glycerin. In addition, an emulsion-type lotion is also disclosed in Japanese Examined Patent Publication No. 3-68009 that contains 1 α ,24-dihydroxyvitamin D₃, an oil phase compo-

50 nent comprising a solid oil component such as stearyl alcohol and a liquid oil component such as liquid paraffin, and a surfactant comprising sodium laurylsulfate.

[0009] If these emulsion-type lotions are, for example, stored in an environment of 50°C or lower or stimulated by vibration, a change in viscosity occurs and the gelation is observed.

5 [0010] Namely, conventional active vitamin D₃ emulsion lotions are not always satisfactory with respect to the point of pharmacological activity and chemical stability of the primary drug, the point of having optimum viscosity with respect to, for example, not sticking to areas of (the) hair, being easily applied and not running easily, the point of feel during application, and the point of physical stability of the preparation when subjected to long-term storage, heat or vibrations etc.

10 Disclosure of the Invention

[0011] Namely, the object of the present invention is to provide an active vitamin D₃ emulsion lotion in which the pharmacological activity and chemical stability of the primary drug in the form of active vitamin D₃ are retained.

15 [0012] Moreover, another object of the present invention is to provide an active vitamin D₃ emulsion lotion that retains the pharmacological activity and chemical stability of the primary drug in the form of active vitamin D₃, and/or has excellent pharmacological activity and chemical stability, and has a viscosity suitable for application to, for example, areas of (the) hair.

20 [0013] Moreover, still another object of the present invention is to provide an active vitamin D₃ emulsion lotion that retains the pharmacological activity and chemical stability of the primary drug in the form of active vitamin D₃, and/or has excellent pharmacological activity and chemical stability, has a viscosity suitable for application to, for example, areas of (the) hair, has excellent physical stability with respect to subjecting the preparation to long-term storage, heat or vibrations, and has a low level of skin irritability.

25 [0014] In consideration of the above-mentioned objects, as a result of conducting earnest studies to develop an active vitamin D₃ oil-in-water (O/W) type of emulsion lotion that satisfies the conditions of (1) not sticking, being easily applied and having a viscosity that prevents running even when applied to areas of (the) hair, (2) retaining pharmacological activity and chemical stability of active vitamin D₃ sufficient for use as a pharmaceutical, (3) having sufficient physical stability for use as a pharmaceutical, and (4) having a low level of irritability to the skin, the inventors of the present Invention found that the above-mentioned objects can be achieved by combining the use of a specific oil phase component, the addition of an ionic polysaccharide to an aqueous phase component, the use of a nonionic surfactant, as well as the use of the specific content of said ionic surfactant, the specific content of a higher alcohol in the oil phase component and of the specific HLB of said nonionic surfactant, thereby leading to completion of the present Invention.

30 [0015] Namely, the present invention provides an active vitamin D₃ emulsion lotion, for example for treatment of skin disease, containing:

35 (a) a therapeutically effective amount of active vitamin D₃,
 (b) an oil phase component containing a solid oil component comprising white Petrolatum and a higher alcohol, and a liquid oil component comprising squalane,
 (c) an aqueous phase component containing ionic polysaccharide, and
 40 (d) nonionic surfactant; wherein,

(1) the content of said ionic polysaccharide is 0.3 to 1.0 parts by weight of the entire preparation,
 (2) the content of said higher alcohol is 0.2 to 1.0 parts by weight of the entire preparation, and
 (3) the HLB of said nonionic surfactant is 10 or more.

45 Brief Description of the Drawings

[0016]

50 Fig. 1 is a flow chart indicating an example of the manufacturing process of lotions of the present invention.
 Fig. 2 is a graph showing the results of a cumulative skin irritation test in rabbits for the lotion of Example 1 of the present invention and the lotions of Comparative Examples 9 and 10.

Mode for Carrying Out the Invention

55 [0017] The oil phase component that forms an active vitamin D₃ lotion of the present invention contains a solid oil component comprising white Petrolatum and higher alcohol, and a liquid oil component comprising squalane.

[0018] The white Petrolatum of the present invention is purified by decoloring a mixture of hydrocarbons obtained from

petroleum, and the quality standards stipulated in, for example, the Japanese Pharmacopoeia, are used for its quality standards. In particular, the white Petrolatum having high purity is preferable for the stability of active vitamin D₃, for example, 1 α ,24-dihydroxyvitamin D₃, and that having, for example, a peroxide value of 0.5 or less is preferable.

[0019] In addition, the squalane of the present invention is a saturated hydrocarbon obtained by, for example, reducing hydrocarbons obtained from the liver oil of sharks residing deep in the ocean, and the quality standards stipulated in, for example, Japanese Cosmetic Raw Material Standards are used for its quality standards.

[0020] The hydrocarbon-based oil phase component described above has been confirmed to have lower irritability as compared with polar oil phase components such as fatty acid esters in a skin primary irritation test in rabbits conducted by the inventors of the present invention. The use of this oil phase component with a low level of irritability makes it possible to obtain a lotion having a low level of irritability and capable of be applied to the affected area of the skin such as in psoriasis.

[0021] Here, it is preferable that the higher alcohol content of the present invention be 0.2 to 1.0 parts by weight of the entire preparation. If the amount is greater than 1.0 parts by weight, it tends to be difficult to obtain a lotion that is free of changes in viscosity caused by the environment such as heat or vibrations. In addition, if the amount is less than 0.2 parts by weight, it becomes difficult to form a protective layer (phase D) around the oil phase. This results in greater susceptibility to the occurrence of phase separation of the oil and aqueous phases, eventually tending to significantly lower the chemical stability of the active vitamin D₃.

[0022] Here, a preferable example of the viscosity of the lotion of the present invention is a lotion viscosity of 500 to 1400 mPa.s when measured with a Brookfield rotational viscometer using a spindle no. LV4, at 60 rpm and 25°C.

[0023] More specifically, the contents of the white Petrolatum, higher alcohol and squalane that form the oil phase component of the present invention preferably form a solid oil component comprising 2 to 5 parts by weight of white Petrolatum and 0.2 to 0.5 parts by weight of higher alcohol, and a liquid oil component comprising 1 to 2.5 parts by weight of squalane within a range that satisfies the above-mentioned weight ratio of the solid oil component and liquid oil component.

[0024] In addition to white Petrolatum, higher alcohol and squalane as mentioned above, other solid oil and liquid oil components may be added to the oil phase component of the present invention. Examples of solid oil components include solid paraffin, spermaceti wax and beeswax. Their added amounts should be within the range that allows one of the objects of the present invention, for example physical stability, to be maintained. As examples of the amounts added, an amount of 1/4 the parts by weight or less of the solid oil component of the present invention is preferable for being able to maintain the viscosity of a lotion that is suitable for application to sites where there is (the) hair. Examples of the liquid oil component include esters such as medium chain fatty acid triglycerides, diisopropyladipate and isopropylmyristate, liquid paraffin, and dimethylpolysiloxane. The amounts of these liquid oil components added should be within the range in which one of the objects of the present invention, for example physical stability, is maintained. For example, an amount of 1/2 the parts by weight or less of the squalane of the present invention is preferable for being able to maintain the viscosity of a lotion suitable for application to sites where there is (the) hair. In addition, with respect to irritability, it was found that using an oil phase component other than a hydrocarbon-based oil phase component results in slightly greater irritability than the use of a hydrocarbon-based oil phase component.

[0025] Antioxidant can be added to the oil phase component of the present invention. Examples of antioxidants include butylhydroxytoluene, butylhydroxyanisol and d1- α -tocopherol, while d1- α -tocopherol is added preferably. The amount of said antioxidants is normally 0.001 to 2.0 parts by weight, and more preferably 0.01 to 1.0 parts by weight.

[0026] The aqueous phase component of the present invention contains ionic polysaccharide at a specified concentration. Furthermore, an ionic polysaccharide in the present invention refers to a polysaccharide in which the sugar chain has, for example, a carboxyl group or sulfate group, and has a sugar chain structure that is ionized in aqueous solution. As a result of containing an ionic polysaccharide, the emulsion lotion of the present invention is hardly affected at all by changes in viscosity caused by external stimuli such as heat or vibrations. In addition, it also serves to stabilize the emulsion by preventing phase separation. In addition, even in the case in which active vitamin D₃, the primary drug of the present invention, is unstable in water as with 1 α ,24-dihydroxyvitamin D₃, there is the effect of preventing impairment of the stability of the primary drug.

[0027] Examples of ionic polysaccharide include xanthane gum and/or carrageenan, while xanthane gum is preferable. The content of these ionic polysaccharides is preferably 0.3 to 1.0 parts by weight of the entire preparation, and more preferably 0.4 to 0.8 parts by weight.

[0028] In addition, moisture retention agent, antiseptic, chelating agent, buffer and so forth can be added to the aqueous phase component. Examples of moisture retention agents include propylene glycol, glycerin and sorbitol, and the amount is 1 to 20 parts by weight, and preferably 2 to 15 parts by weight. Examples of antiseptics include parabens such as methylparaben, propylparaben and their mixtures, chlorobutanol, monothioglycerol, sorbic acid, potassium sorbate and benzyl alcohol, and the added amount is 0.001 to 10.0 parts by weight, and preferably 0.01 to 5.0 parts by weight. Examples of chelating agents include citric acid, sodium citrate and sodium edetate, and the amount is 0.001 to 5.0 parts by weight, and preferably 0.01 to 3.0 parts by weight. Examples of buffers include disodium hydrogenphos-

phate, sodium dihydrogenphosphate and potassium dihydrogenphosphate, and they are added in the required weight ratio for adjusting the pH of the aqueous phase component to 6.5 to 8.5.

[0029] In the lotion of the present invention, the weight ratio of the above-mentioned oil phase component and aqueous phase component (oil phase component/aqueous phase component) is 15/85 to 3/97. If the ratio is outside this range, the previously indicated viscosity and stability preferable for use as a lotion cannot be obtained.

[0030] The active vitamin D₃ lotion of the present invention also contains nonionic surfactant. This nonionic surfactant is comprised of two or more types of surfactants. Examples of such surfactants of the present invention include one or more types of surfactants selected from the group consisting of low HLB surfactants such as sorbitan monooleate, sorbitan monostearate, sorbitan sesquioleate, sorbitan trioleate, glyceryl monostearate, glyceryl monooleate and propylene glycol monostearate, and high HLB surfactants such as polyoxyethylene (30, 40 or 60) sorbitoltetraoleate, polyoxyethylene (20) sorbitan monolaurate, polyoxyethylene (20) sorbitan monopalmitate, polyoxyethylene (20) sorbitan monostearate, polyoxyethylene (20) sorbitan monooleate, polyoxyethylene (10) monolaurate and polyoxyethylene (23, 25 or 30) cetyl ether. Normally, a low HLB surfactant is combined with a high HLB surfactant to adjust HLB for the purpose of stabilizing the emulsion.

[0031] The content of nonionic surfactant of the present invention is preferably 1.8 to 5.2 parts by weight of the entire preparation. Moreover, in this case, it is preferable that the HLB of the overall nonionic surfactant be 10 or more, and preferably 11.0 or more to allow the above-mentioned ionic polysaccharide to demonstrate its phase separation preventive effect. More preferably, the overall content of nonionic surfactant is about 11.5 to 14.5.

[0032] Examples of active vitamin D₃ of the present invention include active vitamin D₃ selected from the group consisting of 1 α ,24-dihydroxyvitamin D₃, 1 α ,25-dihydroxyvitamin D₃ and 1 α -hydroxyvitamin D₃. 1 α ,24(R)-dihydroxyvitamin D₃ and 1 α ,24(S)-dihydroxyvitamin D₃ are preferable, while 1 α ,24(R)-dihydroxyvitamin D₃ is particularly preferable due to its excellent pharmacological activity. In addition, crystals of 1 α ,24(R)-dihydroxyvitamin D₃ are preferable in terms of purity, and, for example, its 1 hydrate form can be used.

[0033] The amount of active vitamin D₃ of the present invention is the dose that is effective for treating the skin disease for which it is applied, and normally is within the range of about 0.00005 to 0.01 parts by weight as the concentration in the lotion.

[0034] The active vitamin D₃ lotion of the present invention is produced in accordance with routine methods by dissolving a required amount of active vitamin D₃ in an oil phase component with surfactant with heating; mixing the solution with the aqueous phase component or aqueous phase component excluding the ionic polysaccharide solution, that has been heated in an emulsifying machine; emulsifying the mixture to form a uniform emulsion, or adding the ionic polysaccharide solution to the mixture as necessary and then emulsifying the mixture to form a uniform emulsion; and finally cooling.

[0035] The active vitamin D₃ lotion of the present invention can be used as a therapeutic agent for skin diseases such as psoriasis vulgaris, pustular psoriasis, psoriasis guttata, erythrokeratoderma, psoriasis arthropila, psoriasis gravis and other types of psoriasis and keratosis. Although the dosage varies according to the severity of the disease and so forth, it is preferable, for example, to administer a lotion having a concentration of 1 α ,24-dihydroxyvitamin D₃ of 100 to 0.1 μ g/g of lotion once to several times daily to the affected area. Thus, an emulsion lotion is provided that contains active vitamin D₃, has a viscosity that is suitable for application to a site where there is (the) hair, has satisfactory pharmacological activity, stability of the primary drug and physical stability, and has a low level of skin irritability. In addition, the significance of providing this active vitamin D₃ emulsion lotion for the clinical setting is extremely great.

Examples

[0036] Although the following provides a further explanation of the present invention through its examples, it goes without saying that the present invention is by no means limited to these examples. An explanation is first provided regarding the various types of test methods used in the examples.

Summary of Description and Purposes of Testing

[0037] The contents and purposes of tests performed are described in Table 1.

Table 1

Contents and Purposes of Tests Performed		
Test No.	Description	Purpose
Test Method 1	Lotion viscosity evaluation test Measurement of viscosity using a rotational viscometer	Evaluation of viscosity
Reference Test 1	Evaluation of viscosity by a sensory test	Determination of optimum viscosity range
Test Method 2	Lotion physical stability tests 2-1 Gravitational load test (centrifugal phase separation test) 2-2 Thermal load test (storage at 40 to 50°C)	Evaluation of physical stability of emulsion according to presence of phase separation or gelation
Test Method 3	Lotion primary drug chemical stability test Measurement of primary drug residual rate by HPLC (storage at 40 to 50°C)	Evaluation of chemical stability
Test Method 4	Lotion pharmacological activity test ODC inhibitory activity test	Evaluation of pharmacological activity of preparation
Test Method 5	Lotion skin irritation test Comparative cumulative skin irritation test using rabbits	Evaluation of safety (irritability) of preparation

[0038] The following provides a detailed description of the test methods relating to Table 1.

Test Method 1: Lotion Viscosity Test Method

[0039] A sample lotion was filled into glass screw-top tube (Maruem, No. 3L) having a diameter of 21 mm, mouth diameter of 12 mm and depth of 50 mm up to the threads so as not to allow entrance of bubbles. Testing was performed in an environment at 25°C under the following conditions in compliance with the provisions of the Japanese Pharmacopoeia General Test Methods, Viscosity Measurement Method, Method No. 2: Rotational Viscometer Method.

Test Conditions:

[0040]

Apparatus: Single cylinder rotational viscometer DV-II+
(Brookfield)

Rotor: LV4 rotor

Speed: 60 rpm

Measurement: Viscosity was measured after rotating the rotor for 3 minutes.

[0041] Evaluation criterion was based on taking a viscosity of 500 to 1400 mPa·s to be the optimum viscosity (see Reference Test 1).

Reference Test 1: Viscosity Evaluation of Lotion Using Sensory Tests

[0042] Stickiness and ease of application were evaluated by touch feeling, and resistance to running was evaluated visually for commercially available lotions and test lotions. Furthermore, the commercially available lotions were placed in and pushed out of the containers in which they are sold, while the test lotions were placed in polyethylene containers.

[0043] Evaluation criteria are shown in Table 2, while results are shown in Table 3.

Table 2

Viscosity Evaluation Standards Using Sensory Tests	
Evaluated Parameter	Evaluation Standards
Stickiness	+: Not sticky to the touch feeling and considered not to adhere to (the) hair assuming application to the head. -: Sticky to the touch feeling and considered to easily adhere to (the) hair assuming application to the head.
Ease of application	+: Suitable spreadability and the amount pushed out of the container to be easily adjusted -: Excessive spreadability, considered to be difficult to retain at the affected area, or viscosity too high causing unevenness when pushed out of the container
Resistance to running	+: Little risk of entering the eyes due to running assuming application to the head. -: High risk of entering the eyes due to running assuming application to the head.

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Table 3

Evaluation of Viscosity by Sensory Tests					
Lotion	Viscosity (mPa · s)	Stickiness	Ease of application	Resistance to running	Evaluation
Commercial product A*	80	+	-	-	-
Commercial product B*	270	+	-	-	-
Commercial product C*	590	+	+	+	+
Commercial product D*	760	+	+	+	+
Test preparation A**	1010	+	+	+	+
Commercial product E*	1140	+	+	+	+
Test preparation B**	1380	+	+	+	+
Test preparation C**	1520	+	-	+	-
Test preparation D**	1850	-	-	+	-

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Commercial products A through D were as indicated below.

Commercial Product A: Nippon Glaxo, Deltamovate Scalp Lotion

Commercial Product B: Shionogi Pharmaceuticals, Rinderon V Lotion

Commercial Product C: Tanabe Pharmaceuticals, Topsym Lotion

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Commercial Product D: Taiho Pharmaceuticals, Pandal Lotion

Commercial Product E: Kowa Shinyaku, Lidomex Lotion

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** Test preparations A through D were as shown in Table 4.

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Table 4

Ingredient	Test A (Example 1)	Test preparation B	Test preparation C	Test preparation D
1 α ,24-dihydroxyvitamin D ₃	0.0002	-	-	-
d1- α -tocopherol	0.02	-	-	-
Diisopropyladipate	0.5	0.5	0.5	0.5
White Petrolatum	3.5	-	-	3.4
Paraffin	0.7	0.35	0.35	0.7
Stearyl alcohol	0.3	0.35	0.35	0.3
Squalane	1.7	-	-	1.7
Fatty acid triglyceride	-	4.5	4.5	-
Liquid paraffin	-	5.0	5.0	-
Glyceryl monostearate	0.6	1.0	1.0	1.6
Polyoxyethylene hydrogenated castor oil 60	1.0	1.0	1.0	0.5
Polyoxyethylene (23) cetyl alcohol	1.0	1.0	1.0	0.5
Hydroxymethylbenzoate	0.1	0.1	0.1	0.1
Hydroxypropylbenzoate	0.05	0.05	0.05	0.05
Sodium citrate	0.57	0.57	0.57	0.57
Propylene glycol	10	10	-	10
Butylene glycol	-	-	10	-
Glycerol	-	-	-	-
Disodium hydrogenphosphate	Suitable amount	Suitable amount	Suitable amount	Suitable amount
Potassium dihydrogenphosphate	Suitable amount	Suitable amount	Suitable amount	Suitable amount
Hydroxyethylcellulose	-	-	0.3	-
Xanthane gum	0.6	0.6	0.6	0.6
Purified water	Suitable amount	Suitable amount	Suitable amount	Suitable amount
Total	100	100	100	100
HLB	13	11.7	11.7	8

* Units: parts by weight

* Total parts by weight was adjusted with purified water.

[0044] According to the results of Table 2, the optimum viscosity for efficiently reaching the affected area, safety and easy handling as an externally applied medication for skin diseases that is applied to areas of (the) hair and so forth was found to be 500 to 1400 mPa · s.

Test Method 2: Lotion Physical Stability Test Methods

2-1 Gravitational Load Test

[0045] One g of sample lotion was placed in a centrifuge tube and removed after centrifuging for 1 hour at about 3750 rpm. The appearance of the lotion was observed and checked for the presence of separation of the oil and aqueous

phases.

[0046] The evaluation criteria were the absence of phase separation and spots.

2-2 Thermal Load Test (Heating Test)

[0047] Eight g of sample lotion was placed in a glass sample tube. The tube was sealed and then stored in a constant temperature bath at 50°C or 40°C. Observation of lotion appearance and measurement of viscosity were performed over time, and the lotion was checked for the presence of separation between the oil and aqueous phases as well as for changes in viscosity.

[0048] The evaluation criteria were the absence of phase separation and spots.

Test Method 3: Lotion 1 α ,24-dihydroxyvitamin D₃ Chemical Stability Test Method

[0049] 500 mg of lotion were placed in a centrifuge tube followed by the addition of 50 μ l of internal standard (prednisolone 100 μ g/ml) and 5 ml of dichloromethane, after which the sample was centrifuged for 10 minutes at 3000 rpm while cooling to 5°C after shaking for 10 minutes. The bottom dichloromethane layer was removed, and a portion was injected into an HPLC to determine the amount of 1 α ,24-dihydroxyvitamin D₃. HPLC conditions were as described below.

20 Column: Inertsil SIL 4.6-250 mm
 Column temperature: 40°C
 Eluent: n-hexane/EtOH (89/11)
 Flow rate: 1 ml/min.
 Detector: UV 265 nm

[0050] Although the evaluation criterion is to judge a residual rate of the primary drug of 95% or more as being stable, in consideration of the measurement error ($\pm 2\%$), a residual rate of 93% or more was judged as being preferable.

Test Method 4: 1 α ,24-dihydroxyvitamin D₃ Lotion Pharmacological Activity Test Method

[0051] The cell growth inhibitory activity of 1 α ,24-dihydroxyvitamin D₃ in a psoriasis animal model was evaluated using ODC (ornithine decarboxylase) activity as a marker of cell growth activity. Namely, epidermal cell growth was accelerated by treating the skin of hairless mice with TPA (12-O-tetradecanoylphorbol-13-acetate) followed by administration of 1 α ,24-dihydroxyvitamin D₃ lotion and measuring inhibition of cell growth in terms of ODC activity. More specifically, 10 nmol of TPA was first administered to a 3 x 3 cm² area of the backs of hairless mice in order to accelerate the growth of epidermal cells. Next, 50 mg of the test sample (lotion) was administered to animals of the dose group at the same site (lotion was not administered to animals of the control group). Five hours later, the skin of the administration site was excised and ODC activity was measured according to the method of Ciba, K., et al. (Cancer Res., 44: 1367-1391 (1984)). The ratio of ODC activity of the dose group to that of the control group was taken to represent the inhibition rate, which was in turn used as an indicator of the pharmacological activity of 1 α ,24-dihydroxyvitamin D₃ lotion.

[0052] The evaluation criterion is to be equivalent to Teijin Bonalpah Ointment (1 α ,24-dihydroxyvitamin D₃ ointment) which was previously marketed and has been used clinically. Furthermore, equivalence refers to that described in biological equivalency testing of Pharmaceutical Manufacturing Guidelines (Yakugyo Jihosha Publishing).

Test Method 5: Comparative Cumulative Skin Irritation Test Method in Rabbits

[0053] 0.05 g of example and comparative example preparations were administered daily for 7 days (occlusive application) to an area of skin on the backs (6.25 cm²) of Japanese white male rabbits followed by evaluation of cumulative irritability (rubor) of the skin according to Dray's evaluation method.

[0054] The evaluation criteria are shown in Table 5. Furthermore, preparations having a score of less than 1 in the results on day 7 were considered to have a low level of irritability.

Table 5

Evaluation Criteria of Comparative Cumulative Skin Irritation Test in Rabbits		
	Degree of Skin Reaction	Score
Erythema Scabbing	No erythema	0
	Very mild erythema (barely recognizable)	1
	Clear erythema	2
	Moderate to severe erythema	3
	Deep red, severe erythema, mild scab formation (impairment of deep tissue)	4
	No edema	0
	Very mild edema	1
Edema	Clear edema	2
	Moderate edema (swelling of about 1 mm)	3
	Severe edema (swelling of more than 1 mm and spreading to surrounding area)	4

Example 1

[0055] The composition prepared as Example 1 is shown in Table 6, while a summary of the production process is shown in Fig. 1.

Table 6

Composition of Example 1		
Primary drug	1. 1 α ,24-dihydroxyvitamin D ₃	0.0002 ppw
Antioxidant	2. d1- α -tocopherol	0.02 ppw
Solvent	3. Diisopropyladipate	0.5 ppw
Solid oil component	4. White Petrolatum	3.5 ppw
	5. Paraffin	0.7 ppw
	6. Stearyl alcohol	0.3 ppw
Liquid oil component	7. Squalane	1.7 ppw
Nonionic surfactant	8. Glyceryl monostearate	0.6 ppw
	9. Polyoxethylene hydrogenated castor oil 60	1 ppw
	10. Polyoxethylene (23) cetyl alcohol	1 ppw
Antiseptic	11. Hydroxymethylbenzoate	0.1 ppw
	12. Hydroxypropylbenzoate	0.05 ppw
Stabilizer	13. Sodium citrate	0.57 ppw
Moisture retention agent	14. Propylene glycol	10 ppw
Ionic polysaccharide	15. Xanthane gum	0.6 ppw
Buffer	16. Disodium hydrogenphosphate	Suitable (pH 7.5)
	17. Sodium dihydrogenphosphate	Suitable (pH 7.5)
Water	18. Purified water	Suitable

Table 6 (continued)

Composition of Example 1		
Total		100 ppw

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Explanation of Preparation Method

[0056] The above-mentioned solid oil component (components 4 to 6), liquid oil component (component 7) and non-ionic surfactant (components 8 to 10) were mixed and heated to 75 to 85°C to form a uniform melt. A solution of 1,α,24-dihydroxyvitamin D₃ (component 1) and antioxidant (component 2) in solvent (component 3) was added to the above mixture followed by heating to uniformly dissolve (Solution A). On the other hand, antiseptic (components 11 and 12), stabilizer (component 13), moisture retention agent (component 14) and buffer (components 16 and 17) were heated to 75-85°C in purified water (component 18) to obtain a uniform solution (Solution B). Ionic polysaccharide (xanthane gum was used as ionic polysaccharide (component 15)) was dissolved in purified water to prepare ionic polysaccharide solution (Solution C).

[0057] Solutions A, B and C were mixed in a vacuum emulsifier (Mizuho) to emulsify and prepare the uniform primary emulsion. This was then cooled to room temperature to obtain a white lotion (Example 1).

[0058] Furthermore, the numbers described for each component shown in Table 2 may be used in place of the names of each component in Example 1 in the following examples and comparative examples. In addition, the examples and comparative examples described herein were prepared in compliance with the above-mentioned production method (Fig. 1) based on Example 1.

Examples 2 to 10 and Comparative Examples 1 to 10

25 [0059] A summary of the examples and comparative examples is shown in Table 7, while the compositions are shown in Tables 8 to 10.

Table 7

Summary of Examples 2 to 10 and Comparative Examples 1 to 10		
No. of Example, Comparative Example	Change in Composition from Example 1	Resulting Findings
Comp. Ex. 1	Amt. of xanthane gum: 0.6 → 0 ppw	Required amount of ionic polysaccharide
Comp. Ex. 2	Amt. of xanthane gum: 0.6 → 0.2 ppw	Optimum amount range of ionic polysaccharide
Example 2	Amt. of xanthane gum: 0.6 → 0.4 ppw	
Example 3	Amt. of xanthane gum: 0.6 → 0.8 ppw	
Comp. Ex. 3	Amt. of xanthane gum: 0.6 → 1.5 ppw	
Example 4	Amt. of stearyl alcohol: 0.3 → 0 ppw	Required amount of stearyl alcohol
Comp. Ex. 4	Amt. of stearyl alcohol: 0.3 → 0.2 ppw	Optimum amount range of stearyl alcohol
Example 5	Amt. of stearyl alcohol: 0.3 → 1.0 ppw	
Comp. Ex. 5	Amt. of stearyl alcohol: 0.3 → 1.2 ppw	
Comp. Ex. 6	HLB: 13 → 8.2	Optimum HLB
Example 6	HLB: 13 → 10	
Comp. Ex. 7	HLB: 13 → 15	

Table 7 (continued)

Summary of Examples 2 to 10 and Comparative Examples 1 to 10		
No. of Example, Comparative Example	Change in Composition from Example 1	Resulting Findings
5 Example 7	Oil phase/aqueous phase ratio: Approx. 10 → 6.5 ppw (surfactant also included in oil phase)	Optimum oil phase/aqueous phase ratio
10 Example 8	Oil phase/aqueous phase ratio: Approx. 10 → 15 ppw (surfactant also included in oil phase)	
15 Comp. Ex. 8	Oil phase/aqueous phase ratio: Approx. 10 → 30 ppw (surfactant also included in oil phase)	
Example 9	Surfactant: 2.6 → 1.8 ppw	Allowed range of amount of surfactant
Example 10	Surfactant: 2.6 → 5.2	
20 Comp. Ex. 9	Use of fatty acid ester in place of Petrolatum (HLB also changes)	Comparison of low irritability of oil phase component
Comp. Ex. 10	Use of fatty acid ester and glycerol in place of Petrolatum (HBL also changes)	

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Table 8

Compositions of Examples and Comparative Examples (Examples 1 to 3 and Comparative Examples 1 to 4)							
Component	Ex. 1	Comp. Ex. 1	Comp. Ex. 2	Ex. 2	Ex. 3	Comp. Ex. 3	Comp. Ex. 4
1 α ,24-dihydroxy-vitamin D ₃	0.0002	0.0002	0.0002	0.0002	0.0002	0.0002	0.0002
d1- α -tocopherol	0.02	0.02	0.02	0.02	0.02	0.02	0.02
Dilisopropyladipate	0.5	0.5	0.5	0.5	0.5	0.5	0.5
White Petroleum	3.5	3.5	3.5	3.5	3.5	3.5	3.5
Paraffin	0.7	0.7	0.7	0.7	0.7	0.7	0.7
Stearyl alcohol	0.3	0.3	0.3	0.3	0.3	0.3	0
Squalane	1.7	1.7	1.7	1.7	1.7	1.7	1.7
Glycerylmonostearate	0.6	0.6	0.6	0.6	0.6	0.6	0.6
Polyoxethylene hydrogenated castor oil 60	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Polyoxethylene (23) cetyl alcohol	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Hydroxymethylbenzoate	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Hydroxypropylbenzoate	0.05	0.05	0.05	0.05	0.05	0.05	0.05
Sodium citrate	0.57	0.57	0.57	0.57	0.57	0.57	0.57
Propylene glycol	10	10	10	10	10	10	10
Disodium hydrogenphosphate	Suitable amount						
Potassium dihydrogenphosphate	Suitable amount						
Xanthane gum	0.6	0	0.2	0.4	0.8	1.5	0.6
Purified water	Suitable amount						
Total	100	100	100	100	100	100	100
HLB	13	13	13	13	13	13	13

* Units: Parts by weight

* Total parts by weight was adjusted with purified water.

Table 9

Compositions of Examples and Comparative Examples (Examples 1 and 4 to 6 and Comparative Examples 5 to 7)								
	Component	Ex. 1	Ex. 4	Ex. 5	Comp. Ex. 5	Comp. Ex. 6	Ex. 6	Comp. Ex. 7
5	1 α ,24-dihydroxy-vitamin D ₃	0.0002	0.0002	0.0002	0.0002	0.0002	0.0002	0.0002
10	d1- α -tocopherol	0.02	0.02	0.02	0.02	0.02	0.02	0.02
15	Diisopropyladipate	0.5	0.5	0.5	0.5	0.5	0.5	0.5
20	White Petrolatum	3.5	3.5	3.5	3.5	3.5	3.5	3.5
25	Paraffin	0.7	0.7	0.7	0.7	0.7	0.7	0.7
30	Stearyl alcohol	0.3	0.2	1.0	1.2	0.3	0.3	0.3
35	Squalane	1.7	1.7	1.7	1.7	1.7	1.7	1.7
40	Glycerylmonostearate	0.6	0.6	0.6	0.6	1.56	1.2	0.2
45	Polyoxyethylene hydrogenated castor oil 60	1.0	1.0	1.0	1.0	0.52	0.7	1.2
Total	Polyoxyethylene (23) cetyl alcohol	1.0	1.0	1.0	1.0	0.52	0.7	1.2
	Hydroxymethylbenzoate	0.1	0.1	0.1	0.1	0.1	0.1	0.1
	Hydroxypropylbenzoate	0.05	0.05	0.05	0.05	0.05	0.05	0.05
	Sodium citrate	0.57	0.57	0.57	0.57	0.57	0.57	0.57
	Propylene glycol	10	10	10	10	10	10	10
	Disodium hydrogenphosphate	Suitable amount						
	Potassium dihydrogenphosphate	Suitable amount						
	Xanthane gum	0.6	0.6	0.6	0.6	0.6	0.6	0.6
	Purified water	Suitable amount						
	HLB	13	13	13	13	8.2	10	15

* Units: Parts by weight

* Total parts by weight was adjusted with purified water.

Table 10

Compositions of Examples and Comparative Examples (Examples 1 and 7 to 10 and Comparative Examples 8 to 10)								
Component	Ex. 1	Ex. 7	Ex. 8	Comp. Ex. 8	Ex. 9	Ex. 10	Comp. Ex. 9	Comp. Ex. 10
1 α ,24-dihydroxy-vitamin D ₃	0.0002	0.0002	0.0002	0.0002	0.0002	0.0002	0.0002	0.0002
d1- α -tocopherol	0.02	0.01	0.03	0.06	0.02	0.02	0.02	0.02
Diisopropyladipate	0.5	0.35	0.75	1.5	0.5	0.5	0.5	0.5
White Petrolatum	3.5	2.4	5.25	10.5	3.5	3.5	-	-
Paraffin	0.7	0.5	1.05	2.1	0.7	0.7	0.35	0.35
Stearyl alcohol	0.3	0.2	1.5	0.9	0.3	0.3	0.35	0.35
Squalane	1.7	1.2	2.55	5.1	1.7	1.7	1.7	1.7
Fatty acid triglyceride	-	-	-	-	-	-	4.5	4.5
Liquid paraffin	-	-	-	-	-	-	5.0	5.0
Glycerylmonostearate	0.6	0.42	0.9	1.8	0.42	1.2	1.0	1.0
Polyoxyethylene hydrogenated castor oil 60	1.0	0.69	1.5	3.0	0.69	2.0	1.0	1.0
Polyoxyethylene (23) cetyl alcohol	1.0	0.69	1.5	3.0	0.69	2.0	1.0	1.0
Hydroxymethylbenzoate	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Hydroxypropylbenzoate	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
Sodium citrate	0.57	0.57	0.57	0.57	0.57	0.57	0.57	0.57
Propylene glycol	10	10	10	10	10	10	10	4
Glycerin	-	-	-	-	-	-	-	6
Disodium Suitable hydrogen-phosphate	amount	Suitable amount	Suitable amount	Suitable amount	Suitable amount	Suitable amount	Suitable amount	Suitable amount
Potassium Suitable dihydrogen-phosphate	amount	Suitable amount	Suitable amount	Suitable amount	Suitable amount	Suitable amount	Suitable amount	Suitable amount
Xanthane gum	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6
Purified water	Suitable amount							
Total	100	100	100	100	100	100	100	100
HLB	13	13	13	13	13	13	11.7	11.7

* Units: Parts by weight

** Total parts by weight was adjusted with purified water.

Physical and Chemical Stability Tests

[0060] The physical stability of the lotions of Examples 1 through 10 and Comparative Examples 1 through 10 was determined by test methods 1 and 2, while their chemical stability was determined by test method 3. The evaluation criteria are shown in Table 11, and the results are shown in Table 12.

Table 11 Physical and Chemical Stability Test Evaluation

Criteria

Test Parameter	Evaluation Criteria
Viscosity Test	<ul style="list-style-type: none"> +: Viscosity within the range of 500 to 1400 mPa·s when measured according to test method 1. -: Viscosity less than or greater than 500 to 1400 mPa·s when measured according to test method 1.
Gravitational Load Test	<ul style="list-style-type: none"> +: No visual observation of phase separation -: Visual observation of phase separation and spots
Thermal Load Test	<ul style="list-style-type: none"> +: No visual observation of phase separation when stored at the temperature and for the duration described in Table 7-2. -: Visual observation of phase separation and spots when stored at the temperature and for the duration described in Table 7-2.
Phase Separation	<ul style="list-style-type: none"> +: No visual observation of gelation when stored at the temperature and for the duration described in Table 7-2, and viscosity no greater than 1400 mPa·s when measured according to test method 1. -: Visual observation of gelation when stored at the temperature and for the duration described in Table 7-2, and viscosity greater than 1400 mPa·s when measured according to test method 1.
Viscosity Change	<ul style="list-style-type: none"> +: Judged to be stable if residual ratio of primary drug is at least 93% when stored at the temperature and duration described in Table 12, and measured according to test method 3. -: Judged to be unstable if residual ratio of primary drug is at least 93% when stored at the temperature and duration described in Table 12, and measured according to test method 1.
Primary Drug Residual Ratio	<ul style="list-style-type: none"> +: Judged to be able to maintain physical and chemical stability as a pharmaceutical. -: Judged to be difficult to retain physical and chemical stability as a pharmaceutical.
Overall Evaluation	<ul style="list-style-type: none"> +: Judged to be able to maintain physical and chemical stability as a pharmaceutical. -: Judged to be difficult to retain physical and chemical stability as a pharmaceutical.

Table 12

Physical and Chemical Stability Results										
Test Parameter	Physical Stability		Thermal Load Test				Chemical Stability		Overall Evaluation	
	Visc. Test	Grav. Load Test	Thermal Load Test				Chemical Stability			
			50°C, 2 weeks	40°C, 3 mos.		50°C, 2 wks.	40°C, 3 mos.			
Ex. 1	+	+	+	+	+	+	95	99	+	
Comp. Ex. 1	-	-	-	+	-	+	90	95	-	
Comp. Ex. 2	-	-	-	+	+	+	92	95	-	
Ex. 2	+	+	+	+	+	+	94	97	+	
Ex. 3	+	+	+	+	+	+	94	97	+	
Comp. Ex. 3	-	+	+	+	+	+	93	96	-	
Comp. Ex. 4	+	+	-	+	+	+	85	92	-	
Ex. 4	+	+	+	+	+	+	93	97	+	
Ex. 5	+	+	+	+	+	+	94	98	+	
Comp. Ex. 5	+	+	+	-	+	-	93	96	-	
Comp. Ex. 6	+	-	-	+	-	+	90	94	-	
Ex. 6	+	+	+	+	+	+	95	98	+	
Comp. Ex. 7	+	-	-	+	-	+	91	95	-	
Ex. 7	+	+	+	+	+	+	93	96	+	
Ex. 8	+	+	+	+	+	+	93	98	+	
Comp. Ex. 8	+	-	-	+	-	+	95	99	-	
Ex. 9	+	+	+	+	+	+	93	94	+	
Ex. 10	+	+	+	+	+	+	93	96	+	
Comp. Ex. 9	+	+	+	+	+	+	94	98	+	
Comp. Ex. 10	+	+	+	+	+	+	94	98	+	

[0061] According to Table 12, those lotions that were judged to be acceptable in the gravitational load and thermal load tests conducted to examine physical stability were Examples 1 through 10 and Comparative Examples 9 and 10. Based on these findings, it was determined that physically stable lotion is obtained due to the synergistic effects of the three factors consisting of weight ratio of higher alcohol, weight ratio of xanthane gum, and HLB of the surfactant.

[0062] In addition, it was also determined that those lotion compositions in which phase separation occurred exhibited very poor chemical stability of 1 α ,24-dihydroxyvitamin D₃ and were unable to maintain stability as a pharmaceutical.

[0063] Furthermore, Comparative Examples 9 and 10 were found to be undesirable in the skin irritation test described below.

Pharmacological Activity Test of Lotion of Example 1

[0064] The results of conducting pharmacological activity tests on the lotion of Example 1 (although the 1 α ,24-dihydroxyvitamin D₃ content in the lotion was 2 μ g/g) and the Bonalpha Ointment of Teljin (active 1 α ,24-dihydroxyvitamin D₃ ointment in which the content of 1 α ,24-dihydroxyvitamin D₃ in the ointment was 2 μ g/g) according to test method 4

are shown in Table 13.

Table 13

Comparison of ODC Activity Inhibition Ratio of Example 1 and Ointment	
Composition	ODC Activity Inhibition Rate
Example 1	26%
Ointment	26%

[0065] Based on Table 13, the lotion of the present invention (Example 1) was determined to exhibit 1 α .24-dihydroxyvitamin D₃ pharmacological activity equal to that of the ointment in an animal model of psoriasis.

Skin Irritation Test of Lotion of Example 1

[0066] The results of conducting a comparative cumulative skin irritation test in rabbits on the lotion of Example 1 (although the content of 1 α .24-dihydroxyvitamin D₃ in the lotion was 2 μ g/g) and the lotion of Comparative Example 9 (wherein the content of 1 α .24-dihydroxyvitaxnin D₃ in the lotion was 2 μ g/g) according to test method 5 are shown in Fig. 2.

Claims

1. An active vitamin D₃ emulsion lotion containing the following components:
 - (a) a therapeutically effective amount of active vitamin D₃,
 - (b) an oil phase component containing a solid oil component comprising white Petrolatum and a higher alcohol and a liquid oil component comprising squalane,
 - (c) an aqueous phase component containing ionic polysaccharide, and
 - (d) nonionic surfactant;
 wherein,
 - (1) the content of said ionic polysaccharide is 0.3 to 1.0 parts by weight of the entire preparation,
 - (2) the content of said higher alcohol is 0.2 to 1.0 parts by weight of the entire preparation, and
 - (3) the HLB of said nonionic surfactant is 10 or more.
2. A lotion as set forth in claim 1 wherein the weight ratio of said oil phase component to said aqueous phase component (oil phase component/aqueous phase component) is 15/85 to 3/97.
3. A lotion as set forth in either of claims 1 or 2 wherein the content of said nonionic surfactant is 1.8 to 5.2 parts by weight of the entire preparation.
4. A lotion as set forth in any of claims 1 through 3 wherein said active vitamin D₃ is an active vitamin D₃ selected from the group consisting of 1 α .24-dihydroxyvitamin D₃, 1 α .25-dihydroxyvitamin D₃ and 1 α -hydroxyvitamin D₃.
5. A lotion as set forth in any of claims 1 through 4 wherein said ionic polysaccharide is xanthane gum and/or carageenan.
6. A lotion as set forth in any of claims 1 through 5 wherein its viscosity is 500-1400 mPa · s when measured with a Brookfield rotational viscometer using a spindle no. LV4 at 60 rpm and 25°C.
7. A lotion as set forth in any of claims 1 through 6 that is a preparation for treatment of skin disease.
8. A lotion as set forth in claim 7 wherein said skin disease is psoriasis or keratosis.

Fig.1

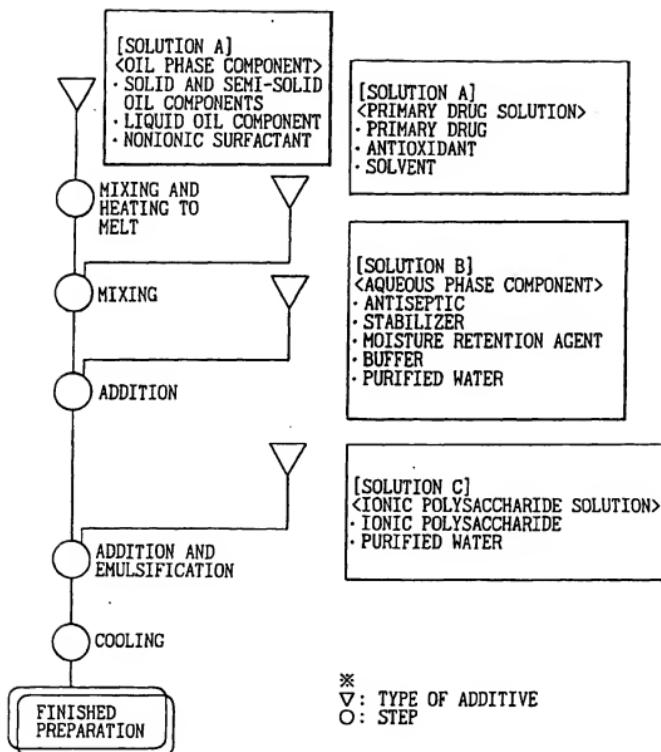
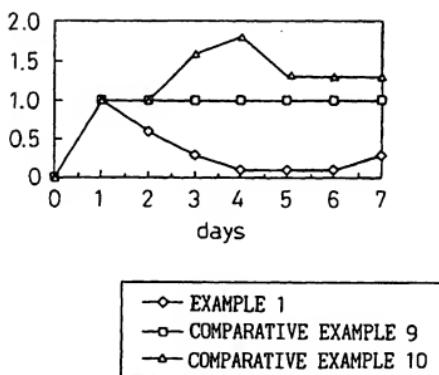


Fig. 2



INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP99/01025

A. CLASSIFICATION OF SUBJECT MATTER		
Int.C1 ⁴ A61K31/59, A61K9/107, A61K47/44, A61K47/36, A61K47/10		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED		
Minimum documentation searched (classification system followed by classification symbols) Int.C1 ⁴ A61K31/59, A61K9/107, A61K47/44, A61K47/36, A61K47/10		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category ⁵	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JP, 7-291868, A (Teijin Ltd.), 7 November, 1995 (07. 11. 95), Claims ; Examples (Family: none)	1-8
A	JP, 9-249555, A (Kowa Co., Ltd.), 22 September, 1997 (22. 09. 97), Claims ; Examples (Family: none)	1-8
A	JP, 4-230317, A (Lion Corp.), 19 August, 1992 (19. 08. 92), Claims ; Examples (Family: none)	1-8
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.		
<p>⁴* Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "B" earlier document but published or on or after the international filing date "C" document which may throw doubt on priority (claim(s) or which is cited to establish the publication date of another citation or other relevant matter (as specified) "D" document referring to an oral disclosure, use, exhibition or other means "E" document published prior to the international filing date but later than the priority date claimed</p> <p>⁵* "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the state of the art or to check for anticipation "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "A" document member of the same patent family</p>		
Date of the actual completion of the international search 24 May, 1999 (24. 05. 99)	Date of mailing of the international search report 1 June, 1999 (01. 06. 99)	
Name and mailing address of the ISA/ Japanese Patent Office	Authorized officer	
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